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EXAMINER
DI NOLA BARON, LILIANA

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1615	

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9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,077	GIDWANI ET AL.	
	Examin r	Art Unit	
	Liliana Di Nola-Baron	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☒ Claim(s) *1-14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 6,7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: on page 4, line 19, the phrase "The film envelop used cane" should be corrected to "The film envelope used can be". On line 20, there is no conjunction between the phrase "can optionally be added" and the phrase "can be used". A verb is missing in the last sentence of p. 4 (lines 23-24). Appropriate correction is required.

Claim Objections

2. Claims 1-14 are objected to because of the following informalities:

a. Claim 1 should read "A monolithic pharmaceutical composition".

b. In claims 1, 4, 5 and 8 the phrase "and or other hydrophobic material" should be written in the alternative form "and/or other hydrophobic material".

c. Claims 2, 3, 6 and 7 should read "The composition of claim 1".

d. Claim 4 should read "The pharmaceutical composition as defined in claim 1"

e. Claim 5 should read "The composition of claim 4".

f. Claim 8 should read "A process of producing".

g. Claims 9 and 10 should read "The process of claim 8".

h. Claims 11 and 12 should read "The process of claim 10".

i. Claim 6 should read "3 to 10% by weight of a binder, 0.5 to 1.5% by weight of a glidant and 0.5 to 1.0% by weight of a lubricant".

j. Claim 7 should read "The composition of claim 1, wherein the pharmaceutical composition is a tablet".

k. In claim 8, the word "compressed" is misspelled.

l. In claim 12, the phrase "up to" is misspelled.

m. Claim 13 should read "of a minimum of 8 hours".

n. In claim 14, the word "antihyperglycemic" is misspelled.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2, 4-6, 8, 9, 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 2 recites the limitation "the sustained release dose" in line 1. There is insufficient antecedent basis for this limitation in the claim, since claim 1 does not read on a sustained release formulation.

6. Regarding claim 5, the phrase "and the like" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "and the like"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

7. Claim 4 recites the limitation "The pharmaceutical formulation as defined in claim 1" in line 1. There is insufficient antecedent basis for this limitation in the claim, since claim 1 reads on a pharmaceutical composition and not on a pharmaceutical formulation.

8. Claim 5 recites the limitation "Composition of claim 4" in line 1. There is insufficient antecedent basis for this limitation in the claim, since claim 4 reads on a pharmaceutical formulation and not on a composition.

9. In claim 6 the phrase "up to 0.5 to 1.5% by weight glidant and up to 0.5 to 1.0% by weight of the lubricant" renders the claim indefinite, because it is not clear what is the percentage range for the glidant and lubricant claimed by Applicant. Furthermore, there is insufficient antecedent basis for the limitation "the lubricant" in line 3 of the claim, since claim 1 does not read on a lubricant.

10. Claim 8 recites the limitation "Process of producing a sustained release metformine hydrochloride composition of claim 1" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, since claim 1 does not read on a sustained release composition.

11. Claim 9 recites the limitation "wherein the aqueous or organic solvent used in the granulation step" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim, since no aqueous or organic solvent is cited in the granulation step claimed in claim 8.

12. Claim 12 recites the limitation "the compacted product" in line 1. There is insufficient antecedent basis for this limitation in the claim, since claim 10 does not read on a compacted product.

13. Claim 14 is directed to the pharmaceutical composition of claim 1, used as oral antihyperglycemic agent, thus the claim provides for the use of the pharmaceutical composition

of claim 1, but, since the claim does not set forth any steps involved in the method/process of use, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

14. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

15. Claim 14 is rejected under 35 U.S.C. 101. Claim 14 is directed to the pharmaceutical composition of claim 1, used as oral antihyperglycemic agent, thus the claim provides for the use of a composition, without specifying the steps involved in the method claimed by Applicant. The claimed use of a composition is directed to non-statutory subject matter, and is therefore unpatentable. The claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). It is suggested that Applicant changes the language of the claim to read on a method of treatment comprising administering the pharmaceutical composition of claim 1.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1, 3, 4, 7, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (WO 99/47125).

Cheng et al. discloses a controlled-release dosage form comprising a homogeneous core comprising metformin hydrochloride and an absorption enhancer, such as a fatty acid (See p. 5, line 19 to p. 6, line 29). Thus, with respect to claims 1 and 4 of the instant application, the international publication provides a homogeneous pharmaceutical composition comprising metformin hydrochloride and a hydrophobic material, specifically a fatty acid, as claimed by Applicant. According to Applicant, a monolithic composition is a homogeneous system (See p. 4, lines 1-6 in the specification), thus the homogeneous composition disclosed by the prior art anticipates the claimed invention.

With regard to claim 3 of the instant application, Example 1 in the international publication provides a core composition comprising 90.54% of metformin hydrochloride, and the most preferred embodiments of the invention comprise 75-95% of the drug (See p. 9, line 3 to p. 10, line 10), thus the international application discloses an amount above the 74% claimed by Applicant.

Regarding claim 7, Cheng et al. teaches that the core of the invention, comprising the drug, the binder and the absorption enhancer is compressed into tablets (See p. 6, lines 16-24 and Example 1), thus the international application provides the pharmaceutical composition in the form of a tablet, as claimed by Applicant.

With respect to claim 13, Cheng et al. teaches that the controlled-release dosage forms of the invention can provide therapeutic levels of the antihyperglycemic drug for 12 to 24 hour period, with peak plasma levels being obtained 8-12 hours after administration (See p.3, line 24 to p. 4, line 9), thus the international application provides a controlled-release composition releasing metformin hydrochloride for more than the 8 hour time period claimed by Applicant. Regarding the immediate release claimed by Applicant, Cheng et al. teaches that the dosage form of the invention may comprise an effective amount of the antihyperglycemic drug that is available for immediate release (See p. 8, line 33 to p. 9, line 2), and the preferred antihyperglycemic drug is metformin hydrochloride (See p. 5, lines 23-26), thus the international application provides a composition, which releases metformin hydrochloride immediately after administration, as claimed by Applicant.

With regard to claim 14, Cheng et al. provides tablets comprising metformin hydrochloride and an absorption agent for oral administration (See p. 16, Table 1, lines 7-19 and Figures 4-8) and teaches that the drugs of the invention, including metformin hydrochloride, are useful in controlling or managing noninsulin-dependent diabetes mellitus (See p. 5, lines 20-26).

The compositions disclosed by Cheng et al. meet the limitations of claims 1, 3, 4, 7, 13 and 14 of the instant application, as the international application contemplates controlled-release pharmaceutical compositions comprising metformin hydrochloride and hydrophobic material in the form of tablets. Thus, the international application anticipates the claimed invention.

18. Claims 1 and 3-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Saslawski et al. (WO 99/42086).

The international publication provides compositions comprising an active ingredient and an absorption-promoting agent, and includes esters of fatty acids, fatty alcohols and fatty acids as absorption-promoting agents (See p. 3, lines 17-35) and metformiine hydrochloride as active ingredient (See p. 11, line 35 to p. 12, line 2 and p. 13, lines 1-3). Additionally, the international publication teaches that the compositions of the invention may be in the form of monolithic gelatin capsule (See p. 17, lines 34-37 and p. 19, lines 15-25). Thus, with regard to claims 1 and 4 of the instant application, the international publication discloses monolithic pharmaceutical compositions comprising metformin hydrochloride as active agent and fatty acids, fatty alcohols and esters of fatty acids as hydrophobic material, as claimed by Applicant.

With respect to claim 3, the international application teaches that the amount of active ingredient present in the compositions of the invention is 0.001-95% (See p. 13, lines 7-10), thus meeting the limitation of at least 74% claimed by Applicant.

Regarding claim 5, the international publication discloses glyceryl monostearate , glyceryl palmitostearate, glyceryl monooleate, stearic acid and cetyl alcohol among the lipid (hydrophobic) substances used in the invention (See p. 8, lines 18-31), as claimed by Applicant.

The compositions disclosed by Saslawski et al. meet the limitations of claims 1 and 3-5 of the instant application, as the international application contemplates monolithic pharmaceutical compositions comprising metformin hydrochloride and hydrophobic material. Thus, the international application anticipates the claimed invention.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

19. Claims 1, 3-5, 7 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Berner et al. (U.S. Patent 6,488,962).

The patent provides a controlled-release oral monolithic dosage form comprising metformin hydrochloride (See claims 1 and 25) and hydrophobic additives, including fatty acids and glyceryl monostearate (See col. 7, lines 56-66). Thus, with respect to claims 1, 4 and 5 of the instant application, the patent discloses monolithic pharmaceutical compositions comprising metformin hydrochloride and a hydrophobic substance, including fatty acids and glyceryl monostearate, as claimed by Applicant.

Regarding claim 3, the patent teaches that the drug constitutes 1-98% by weight of the dosage form, thus it contemplates an amount of at least 74%, as claimed by Applicant.

With regard to claim 7, the patent teaches that the oral dosage forms of the invention are in the form of tablets (See col. 6, lines 39-62).

With respect to claim 14, the patent provides oral dosage forms of the drug, which have a therapeutic effect in the treatment of a disease (See col. 7, lines 32-59). The antihyperglycemic effect claimed by Applicant is inherent to the composition.

The compositions disclosed by Berner et al. meet the limitations of claims 1, 3-5, 7 and 14 of the instant application, as the patent contemplates controlled-release oral monolithic pharmaceutical compositions comprising metformin hydrochloride and hydrophobic material, and their use in therapeutic treatment. Thus, the patent anticipates the claimed invention.

20. Claims 1, 3, 4, 7, 13 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Cheng et al. (U.S. Patent 6,099,859).

Cheng et al. discloses a controlled-release dosage form comprising a homogeneous core comprising metformin hydrochloride and an absorption enhancer, such as a fatty acid (See col. 3, line 31 to col. 4, line 12). Thus, with respect to claims 1 and 4 of the instant application, the

patent provides a homogeneous pharmaceutical composition comprising metformin hydrochloride and a hydrophobic material, specifically a fatty acid, as claimed by Applicant. According to Applicant, a monolithic composition is a homogeneous system (See p. 4, lines 1-6 in the specification), thus the homogeneous composition disclosed by the prior art anticipates the claimed invention.

With regard to claim 3 of the instant application, Example 1 in the patent provides a core composition comprising 90.54% of metformin hydrochloride, and the most preferred embodiments of the invention comprise 75-95% of the drug (See col. 5, lines 27-42), thus the patent discloses an amount above the 74% claimed by Applicant.

Regarding claim 7, Cheng et al. teaches that the core of the invention, comprising the drug, the binder and the absorption agent is compressed into tablets (See col. 3, line 66 to col. 4, line 7 and Example 1), thus the patent provides the pharmaceutical composition in the form of a tablet, as claimed by Applicant.

With respect to claim 13, Cheng et al. teaches that the controlled-release dosage forms of the invention can provide therapeutic levels of the antihyperglycemic drug for 12 to 24 hour period, with peak plasma levels being obtained 8-12 hours after administration (See col. 2, lines 34-55), thus the patent provides a controlled-release composition releasing metformin hydrochloride for more than the 8 hour time period claimed by Applicant. Regarding the immediate release claimed by Applicant, Cheng et al. teaches that the dosage form of the invention may comprise

an effective amount of the antihyperglycemic drug that is available for immediate release (See col. 5, lines 20-26), and the preferred antihyperglycemic drug is metformin hydrochloride (See col. 3, lines 36-38), thus the patent provides a composition, which releases metformin hydrochloride immediately after administration, as claimed by Applicant.

With regard to claim 14, Cheng et al. provides tablets comprising metformin hydrochloride and an absorption agent for oral administration (See col. 9, Table 1, lines 22-51 and Figures 4-8) and teaches that the drugs of the invention, including metformin hydrochloride, are useful in controlling or managing noninsulin-dependent diabetes mellitus (See col. 3, lines 33-38).

The compositions disclosed by Cheng et al. meet the limitations of claims 1, 3, 4, 7, 13 and 14 of the instant application, as the patent contemplates controlled-release pharmaceutical compositions comprising metformin hydrochloride and hydrophobic material in the form of tablets. Thus, the patent anticipates the claimed invention.

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claims 1, 3-5, 7 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Berner et al. (U.S. Patent 6,488,962).

The patent provides a controlled-release oral monolithic dosage form comprising metformin hydrochloride (See claims 1 and 25) and hydrophobic additives, including fatty acids and glyceryl monostearate (See col. 7, lines 56-66). Thus, with respect to claims 1, 4 and 5 of the

instant application, the patent discloses monolithic pharmaceutical compositions comprising metformin hydrochloride and a hydrophobic substance, including fatty acids and glyceryl monostearate, as claimed by Applicant.

Regarding claim 3, the patent teaches that the drug constitutes 1-98% by weight of the dosage form, thus it contemplates an amount of at least 74%, as claimed by Applicant.

With regard to claim 7, the patent teaches that the oral dosage forms of the invention are in the form of tablets (See col. 6, lines 39-62).

With respect to claim 14, the patent provides oral dosage forms of the drug, which have a therapeutic effect in the treatment of a disease (See col. 7, lines 32-59). The antihyperglycemic effect claimed by Applicant is inherent to the composition.

The compositions disclosed by Berner et al. meet the limitations of claims 1, 3-5, 7 and 14 of the instant application, as the patent contemplates controlled-release oral monolithic pharmaceutical compositions comprising metformin hydrochloride and hydrophobic material, and their use in therapeutic treatment. Thus, the patent anticipates the claimed invention.

22. Claims 1, 3, 4, 7, 13 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng et al. (U.S. Patent 6,099,859).

Cheng et al. discloses a controlled-release dosage form comprising a homogeneous core comprising metformin hydrochloride and an absorption enhancer, such as a fatty acid (See col. 3, line 31 to col. 4, line 12). Thus, with respect to claims 1 and 4 of the instant application, the patent provides a homogeneous pharmaceutical composition comprising metformin hydrochloride and a hydrophobic material, specifically a fatty acid, as claimed by Applicant. According to Applicant, a monolithic composition is a homogeneous system (See p. 4, lines 1-6 in the specification), thus the homogeneous composition disclosed by the prior art anticipates the claimed invention.

Regarding claim 7, Cheng et al. teaches that the core of the invention, comprising the drug, the binder and the absorption agent is compressed into tablets (See col. 3, line 66 to col. 4, line 7 and Example 1), thus the patent provides the pharmaceutical composition in the form of a tablet, as claimed by Applicant.

With respect to claim 13, Cheng et al. teaches that the controlled-release dosage forms of the invention can provide therapeutic levels of the antihyperglycemic drug for 12 to 24 hour period, with peak plasma levels being obtained 8-12 hours after administration (See col. 2, lines 34-55), thus the patent provides a controlled-release composition releasing metformin hydrochloride for more than the 8 hour time period claimed by Applicant. Regarding the immediate release claimed by Applicant, Cheng et al. teaches that the dosage form of the invention may comprise an effective amount of the antihyperglycemic drug that is available for immediate release (See col. 5, lines 20-26), and the preferred antihyperglycemic drug is metformin hydrochloride (See

col. 3, lines 36-38), thus the patent provides a composition, which releases metformin hydrochloride immediately after administration, as claimed by Applicant.

With regard to claim 14, Cheng et al. provides tablets comprising metformin hydrochloride and an absorption agent for oral administration (See col. 9, Table 1, lines 22-51 and Figures 4-8) and teaches that the drugs of the invention, including metformin hydrochloride, are useful in controlling or managing noninsulin-dependent diabetes mellitus (See col. 3, lines 33-38).

The compositions disclosed by Cheng et al. meet the limitations of claims 1, 3, 4, 7, 13 and 14 of the instant application, as the patent contemplates controlled-release pharmaceutical compositions comprising metformin hydrochloride and hydrophobic material in the form of tablets. Thus, the patent anticipates the claimed invention.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 2 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berner et al. (U.S. Patent 6,488,962) in view of Byrd et al. (U.S. Patent 6,197,340).

The teachings of Berner et al. have been summarized above. The patent provides a controlled-release oral monolithic dosage form comprising metformin hydrochloride (See claims 1 and 25) and hydrophobic additives, including fatty acids and glyceryl monostearate (See col. 7, lines 56-66). With respect to claim 2, the patent is deficient in the sense, that it does not disclose an amount of metformin hydrochloride expressed in mg. With regard to claim 6, the patent contemplates the presence of binders, such as hydroxypropyl cellulose, maltodextrin and alginates (See col. 4, line 48 to col. 5, line 55), glidants, such as starch (See col. 5, line 1), and lubricants (See col. 6, line 63 to col. 7, line 8) in the formulations of the invention, however, it fails to disclose the amount of said excipients in the compositions of the invention.

Byrd et al. discloses controlled-release tablets comprising orally effective antidiabetic agents, specifically metformin hydrochloride in an amount of 1000 mg and excipients (See col. 6, line 61 to col. 7, line 34). The typical formulations provided by the patent comprise 1-5% polyvinyl pyrrolidone, a binder, 05-3% of magnesium silicate, a glidant, and 0.5-1.5% of magnesium stearate, a lubricant (See col. 8, lines 34-50 and Examples 10 and 7). Furthermore, Byrd et al. contemplates monolithic systems in the controlled-release technologies encompassed by the invention (See col. 9, lines 24-59).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the compositions disclosed by Berner et al., by including a high dose of metformin hydrochloride in the composition claimed in the instant application, as taught by Byrd et al., and selecting the amount range of the binder, glidant and lubricant in the

pharmaceutical compositions according to the preferred formulations disclosed by Byrd et al. The expected result would have been a successful controlled-release composition comprising metformin hydrochloride. Because of the teachings of Berner et al., that controlled-release oral dosage forms comprising a monolithic composition of metformin hydrochloride and hydrophobic additives may include a binder, glidant and lubricant, and the teachings of Byrd et al., that high doses of metformin hydrochloride may be loaded in controlled-release formulations for administration to diabetic patients, and said controlled-release formulations should include a binder, glidant and lubricant in specific amounts, one of ordinary skill in the art would have a reasonable expectation that the compositions claimed in the instant application would be successful controlled-release pharmaceutical compositions of metformin hydrochloride. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

25. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (U.S. Patent 6,099,859).

Cheng et al. discloses a controlled-release dosage form comprising a homogeneous core comprising metformin hydrochloride, preferably 3-15% of a binder and an absorption enhancer, such as a fatty acid, and teaches that the core is formed by granulating the core ingredients and compressing the granules with the addition of a lubricant, and coated with a polymeric membrane (See col. 3, line 33 to col. 4, line 12).

With respect to claim 8 of the instant application, the process disclosed in Example 1 of the patent teaches that metformin hydrochloride is granulated in a granulator with a binder at a temperature of 50-70°C, and the granules are then dried (See col. 6, lines 19-33). Thus, the patent contemplates hot melt granulation and drying, as claimed by Applicant. The example does not specifically include a fatty acid as absorption enhancer in the granulating mixture, however, in its preferred embodiment the patent contemplates the presence of an absorption enhancer in the core (See col. 5, lines 27-42). Furthermore, the patent contemplates the presence of excipients in the formulations of the invention (See col. 5, lines 60-67). Thus, one of ordinary skill in the art would granulate a mixture comprising the metformin hydrochloride and the fatty acid to obtain the most preferred formulation according to the teachings of Cheng et al.

Regarding claim 9, the patent teaches that the binder, povidone, is dissolved in purified water and the binding solution is sprayed on metformin hydrochloride in the granulator (See col. 6, lines 22-29), thus the aqueous solvent used in the granulation contains the binder, as claimed by Applicant.

Regarding claim 10, the patent teaches that the granules of metformin hydrochloride obtained from the granulation process are compressed on a rotary press (See col. 6, lines 34-40), thus the process disclosed by the patent includes the step of compressing the dry granules, as claimed by Applicant.

With respect to claim 11, Cheng et al. includes the step of coating the core tablets with a sustained releasing coating (See step d in Example 1) and teaches that the homogeneous core is coated with a polymeric membrane made of cellulose derivatives and optionally comprising a flux enhancing agent, such as sucrose, sorbitol and mannitol (See col. 4, lines 10-43). Thus, the patent provides the general teachings, that tablets comprising metformin hydrochloride and formed by granulation and compression are coated with a polymeric film. The patent is deficient in the sense, that it does not specifically teach that the coating masks the drug taste. On page 4 of the specification, Applicant states that the film envelop used for taste neutralization in the claimed invention can be made of cellulose derivatives. Thus, the polymeric membrane made of cellulose derivative disclosed by the prior art should neutralize the taste of the drug. Furthermore it is the view of the examiner, that the sugars in the coating disclosed by Cheng et al. would naturally mask the taste of the drug.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Cheng et al., in order to produce a sustained-release formulation comprising metformin hydrochloride. The expected result would have been a successful process for producing controlled-release tablets comprising metformin hydrochloride. Because of the teachings of Cheng et al., that homogeneous granule cores comprising metformin hydrochloride may be formed in a granulator at high temperature, dried and compressed into tablets, and the tablets may be coated, one of ordinary skill in the art would have a reasonable expectation that the process claimed in the instant application would be successful in producing controlled-release pharmaceutical compositions of metformin hydrochloride. Therefore the

invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

26. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al (U.S. Patent 6,099,859) as applied to claims 8-11 above, and further in view of Byrd et al. (U.S. Patent 6,197,340).

The teachings of Cheng et al. have been summarized above. Cheng et al. discloses a process for producing a controlled-release tablet containing 90.54% of metformin hydrochloride, 4.38% of povidone, a binder, and 0.5% of magnesium stearate, a lubricant (See Example 1). Thus, with respect to claim 12, Cheng et al. discloses a process comprising up to 1.5% of lubricant and up to 4.5% of binder, as claimed by Applicant. Cheng et al. contemplates the presence of various excipients and lubricants in forming the tablets of the invention (See col. 5, lines 60-67), however, the patent is deficient in the sense, that it does not specifically provide a glidant in the process of the invention, as claimed by Applicant.

Byrd et al. discloses controlled-release tablets comprising orally effective antidiabetic agents, specifically metformin hydrochloride in an amount of 1000 mg and excipients (See col. 6, line 61 to col. 7, line 34). The typical formulations provided by the patent comprise 1-5% polyvinyl pyrrolidone, a binder, 05-3% of magnesium silicate, a glidant, and 0.5-1.5% of magnesium stearate, a lubricant (See col. 8, lines 34-50). In Example 10, Byrd et al. discloses formulations

comprising metformin hydrochloride and prepared by a granulation process in the presence of 3% of povidone, a binder, 1% of talc, a glidant, and 0.5% of magnesium stearate, a lubricant (See Examples 10 and 7).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the process and formulations disclosed by Cheng et al., by including a glidant in the formulations of the invention, as taught by Byrd et al., to improve the sustained-release properties of the tablets comprising metformin hydrochloride. The expected result would have been a successful process for producing controlled-release tablets comprising metformin hydrochloride. Because of the teachings of Cheng et al., that homogeneous granule cores comprising metformin hydrochloride may be formed in a granulator at high temperature, dried and compressed into tablets in the presence of a binder and a lubricant, and the teachings of Byrd et al., that preferred formulations comprising metformin hydrochloride include a glidant in an amount of 1% together with a binder and a lubricant, one of ordinary skill in the art would have a reasonable expectation that the process claimed in the instant application would be successful in producing controlled-release pharmaceutical compositions of metformin hydrochloride. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

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August 28, 2003

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